UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICA N.V., and JANSSEN PHARMACEUTICA PRODUCTS, L.P., Plaintiffs and Counterclaim Defendants, v. MYLAN PHARMACEUTICALS INC., Defendant and Counterclaim Plaintiff.	)	Civ. Action No. 2:03-CV-06220 Judge John C. Lifland Magistrate Judge Mark Falk
JANSSEN PHARMACEUTICA N.V. and JANSSEN PHARMACEUTICA PRODUCTS, L.P., Plaintiffs and Counterclaim Defendants, v. DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC., Defendants and Counterclaim Plaintiffs.	)	Civ. Action No. 2:03-CV-06185 Judge John C. Lifland Magistrate Judge Mark Falk ***DOCUMENT ELECTRONICALLY FILED***

DEFENDANTS' POST-TRIAL BRIEF

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I. INTRODUCTION

The obviousness standard to be applied in this case is clearly set forth in numerous Federal Circuit opinions.

> Structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness.

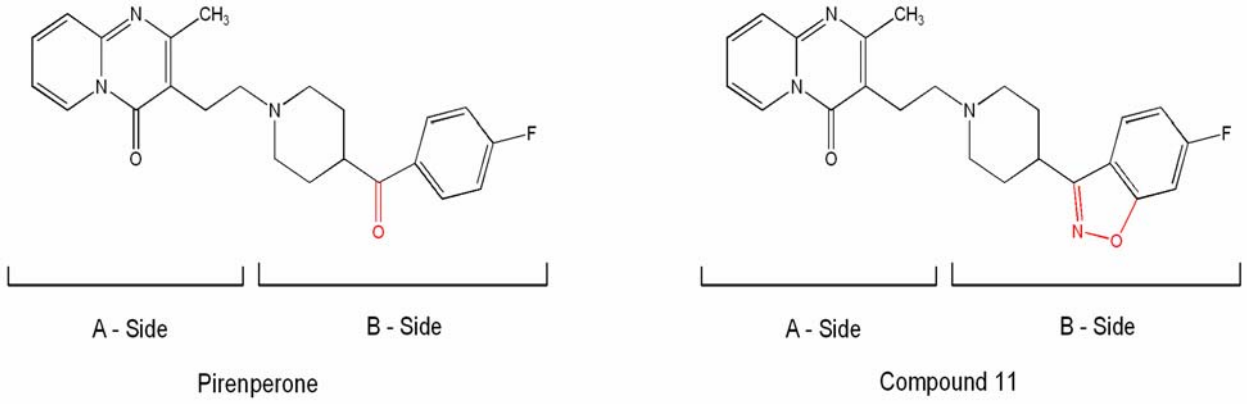
See, e.g., In re Mayne, 104 F.3d 1339, 1342 (Fed. Cir. 1997), citing *In re Dillon,* 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). Defendants established just such a *prima facie* case of obviousness at trial through clear and convincing evidence.

Defendants' obviousness case is a compelling showing directed not at Risperidone, but instead at the "other compound" encompassed by every claim of Janssen's U.S. Patent 4,804,663 ("the '663 patent")—Compound 11. Because Compound 11 is encompassed by each claim, the fact that Compound 11 is obvious renders all of the '663 patent claims invalid.

Defendants' obviousness case is simple—there existed in the prior art the motivation to make a single modification to the structure of Janssen's own prior art compound, Pirenperone. Pirenperone, as so modified, is Compound 11.

Janssen's compound Pirenperone is nearly identical in properties and structure to Compound 11. A structural comparison of Compound 11 and Pirenperone reveals a single difference. For ease of comparison, the structures of

these two compounds are set forth below. For discussion purposes only, each compound has been assigned an "A-side" and a "B-side."



Readily apparent is that the A-side of Pirenperone and Compound 11 are identical. On the B-side, there is but a single difference. Referring to the structure in red, Pirenperone contains what will be referred to herein as a "keto" group.[1] In contrast, Compound 11 includes (highlighted in red) what will be referred to herein as a "benzisoxazole" group.[2]

In addition to Pirenperone's compelling structural similarity to Compound 11, Pirenperone was known in the art to possess properties recognized by those of ordinary skill in the art to be desirable in an antipsychotic.

[1] The "keto" group also may be referred to as a "ketone," "keto moiety" or a "carbonyl" in the present context.
[2] The "benzisoxazole" group may also be referred to as an "isoxazole" group in the present context.

Properties Known to Those of Ordinary Skill in the Art in the Early 1980s to be Desired in an Antipsychotic Drug	
	Pirenperone
1. Dopamine Receptor Antagonist	√
2. Passes Blood-Brain Barrier	√
3. Safe to Use in Humans	√
4. Does Not Cause EPS	√
5. Serotonin Receptor Antagonist	√
6. Long Duration of Action	⊗

Notably, Pirenperone was a potent dopamine antagonist as shown by Janssen's own tests—tests that Janssen told the U.S. Patent and Trademark Office ("USPTO") were *predictive* of a compound's utility as an antipsychotic. Stated simply, Pirenperone possessed those attributes known in the prior art to be desired in a good antipsychotic drug: potent dopamine and serotonin antagonism, the ability to pass through the blood-brain barrier and reach the appropriate chemical receptors in the brain, safe for use in humans, and no extrapyramidal symptoms ("EPS").

Pirenperone had one problem—it suffered from a poor half-life in the body as exhibited by its short duration of action. However, the prior art also taught the likely cause of this short half-life and how to "fix" the problem—with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to replace Pirenperone's keto group with a benzisoxazole group because of Pirenperone's short half-life. We know this to be true because the most likely source of the short

half-life was Pirenperone's keto group, and those skilled in the art would have expected that converting Pirenperone's keto group to a benzisoxazole group would yield a compound having a longer half-life.

Indeed, Janssen was taught by Hoechst-Roussel that benzisoxazoles having similar structures possessed antipsychotic activity. Moreover, the prior art showed that some of those benzisoxazoles with antipsychotic activity were structurally identical to prior art antipsychotic compounds, with the exception that the prior art antipsychotic compound had a keto group rather than a benzisoxazole group. Accordingly, the prior art taught the existence of keto group-containing compounds that had antipsychotic properties *and* that such compounds had benzisoxazole counterparts which also exhibited antipsychotic properties. This is a clear teaching that replacing a keto group in an antipsychotic compound with a benzisoxazole group would have been expected to maintain that compound's antipsychotic activity.

Because Defendants established by clear and convincing evidence a *prima facie* showing of obviousness, the burden shifts to Plaintiffs to rebut this *prima facie* showing. Plaintiffs were free to do so by any means accepted under the guiding principles of *In re Dillon* and its progeny, such as by showing that the claimed compositions possessed unexpectedly improved properties relative to the prior art or that "the prior art is so deficient that there is no motivation to make

what might otherwise appear to be obvious changes." *In re Mayne,* 104 F.3d at 1342, citing *In re Dillon*, 919 F.2d at 692-93.

Plaintiffs apparently chose two approaches. First, they argued that secondary considerations (also referred to as objective indicia) of nonobviousness relative to Risperidone (*e.g.*, commercial success, met a long-felt need, and the like) were sufficient to rebut Defendants' evidence. But such an argument misses the mark. As discussed previously, Defendants are challenging the validity of Compound 11, not Risperidone, and all claims of the '663 patent include Compound 11. A showing of such secondary considerations of nonobviousness relative to Risperidone is legally irrelevant to an obviousness inquiry relating to Compound 11, a compound which is structurally different from Risperidone. Indeed, Plaintiffs did not even attempt to show the existence of secondary considerations relative to Compound 11.

Plaintiffs next presented a shot-gun approach in an apparent attempt to meet their burden of establishing that "the prior art is so deficient that there is no motivation to make what otherwise appears to be obvious changes." Plaintiffs argued: (1) Pirenperone was not an antipsychotic, so there was no motivation for one of skill in the art to modify its structure to develop an antipsychotic, (2) those of ordinary skill in the art would not have been motivated to modify the structure of Pirenperone because it did not possess anticholinergic properties, (3) those of ordinary skill in the art would not have been motivated to modify the structure of

Pirenperone even though it was known that Pirenperone was both a potent dopamine antagonist and a potent serotonin antagonist, because only a portion of those of ordinary skill in the art considered the combination of dopamine and serotonin antagonism to be important in an antipsychotic, and (4) even if one of ordinary skill in the art were motivated to consider Pirenperone when developing an antipsychotic, there were other compounds that one of ordinary skill in the art might also have chosen to modify.

Defendants addressed each of the foregoing positions at trial and demonstrated them to be without merit. Although it is Defendants' position that Plaintiffs have the burden of establishing the veracity of each of these positions, Defendants nevertheless established by clear and convincing evidence that each lacked merit, as set forth in more detail below.

II. THE *PRIMA FACIE* SHOWING OF OBVIOUSNESS

A. Pirenperone's Structure Compared to Compound 11

As discussed above, only a single structural difference separates Compound 11 from the prior art compound Pirenperone. Compound 11 has a benzisoxazole group, while Pirenperone has a keto group. See Defendants' Findings of Fact and Conclusions of Law ("FF/CL") § IV.B.2.a.

B. Pirenperone's Properties Render it Useful as an Antipsychotic

1. Dopamine Antagonist

Janssen has admitted that Pirenperone is a potent dopamine antagonist, and that this fact was known in the prior art. The evidence at trial fully supported this factual conclusion; there was no conflict in the evidence in this regard. *See* FF/CL §§ III.B.1.a. & III.B.2.b.i.

2. Serotonin Antagonist

The evidence at trial was not in conflict. Pirenperone was known in the prior art to be a potent serotonin antagonist. *See* FF/CL §§ III.B.1.b. & III.B.2.b.v.

3. Passes Blood-Brain Barrier

Again, there was no conflict in the evidence. Pirenperone was known in the prior art to pass the blood-brain barrier. *See* FF/CL §§ III.B.1.c. & III.B.2.b.ii.

4. Safe in Humans with no EPS

The prior art also reported that Pirenperone had been used in humans (to treat several hundred patients in need of psychotropic medication) and had shown little or no EPS (side effects) in human clinical studies, thereby assuring its clinical safety (and desirability as a compound). *See* FF/CL §§ III.B.1.c. & III.B.2.b.iii.-iv.

Plaintiffs attempted to raise a factual issue in this regard by introducing an article about the intravenous use of Pirenperone as an analgesic. However, the dosage used in this study was not mentioned in the article. Absent such dosing

information, one would not be able to reach any conclusion regarding EPS, as even Risperidone causes EPS when administered at high dosages. There was no evidence that patients receiving oral doses of Pirenperone for use as a psychotropic ever experienced EPS. *See* FF/CL § III.B.2.b.iv.

C. Pirenperone's Short Half-Life Was Known and Was a Problem

During the development of Pirenperone, Janssen conducted what is referred to as an "emesis" test. In this test, a test compound is administered to a dog, followed by apomorphine. Apomorphine is a compound that induces vomiting in dog by stimulating their dopamine receptors. Depending on the ability of the test compound to prevent (*i.e.,* antagonize) the vomiting of the dog, Janssen was able to predict the test compound's onset and duration of activity in humans. *See* FF/CL § III.B.2.c.

Based on the emesis test results, Pirenperone had a relatively short half-life of only four hours—even at high doses. Janssen even characterized Pirenperone as being "short-acting." Although Janssen attempted to make an issue of this fact, their effort fell far short as nothing conflicted with Janssen's own reports showing Pirenperone's short half-life in Janssen's admittedly predictive dog emesis test. *Id.*

That Pirenperone was short-acting was further confirmed by one of the '663 named inventors, Mr. Kennis. Mr. Kennis testified that the use of Pirenperone in the clinic revealed only a single problem—it had a "metabolic problem" *i.e.,* it

suffered from a short half-life. *See Deposition Transcript of Ludo E.J. Kennis ("Kennis Dep. Tr."), pp. 70, 72.* Mr. Kennis further identified the source of this problem, describing the problem as being due to the fact that the "keto group is reduced to hydroxy function." *Kennis Dep. Tr. p. 69, l. 23 to p. 70, l. 18; p. 71, l. 23 to p. 72, l. 16. See* FF/CL § III.B.2.d. This short half-life was also verified in other studies. *See* FF/CL § III.B.2.c.

For obvious reasons, a compound having a short duration of action (*i.e.*, a short half-life) may not be desirable for use as an antipsychotic outside of a controlled environment, such as a hospital.

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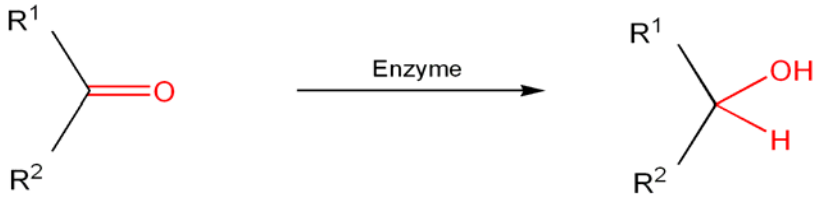
Janssen's position that no one desired an antipsychotic drug that could be administered less than three times a day, and that Pirenperone's half-life was not a problem relative to its development as an antipsychotic, flies in the face of evidence elicited from Janssen's own documents and witnesses, including a named inventor, Mr. Kennis.

D. Identification of the Keto Group as the Source of the Half-Life Problem

The cause of Pirenperone's short half-life is a matter of chemistry. One of skill in the art in the early 1980s, aware of Pirenperone's relatively short half-life, would have been motivated to determine the likely cause of this problem, and then to take steps to alter the structure of Pirenperone to alleviate that problem.

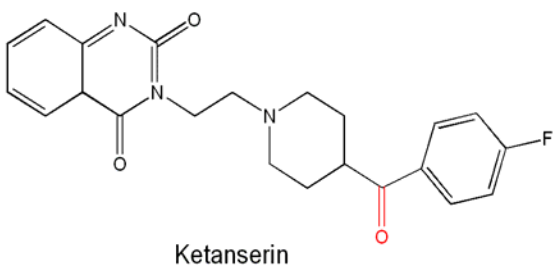
Pirenperone's short half-life problem was not unique. It was well known in the prior art that one chemical group was particularly susceptible to the body's metabolic cycle—the keto group. Pirenperone has just such a keto group. More specifically, it was well known by the early 1980s that keto groups in drugs were susceptible to metabolic "reduction" to alcohols in the human body. An example of this reduction is shown below.



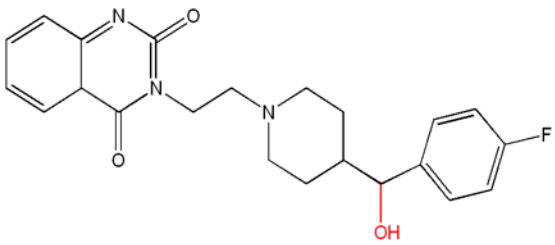
See FF/CL § III.B.2.e.

Further support for the conclusion that one of ordinary skill in the art would have recognized the keto group in Pirenperone to be the source of the short half-life is found in Janssen's own prior art compound, Ketanserin. In the early 1980s, it was known that Ketanserin possessed a keto group, and that this keto group was

extensively metabolized to make "Reduced Ketanserin," also known as Ketanserinol. *Id.*



Ketanserin



Ketanserinol

Although Jansen again attempts to raise a factual issue concerning the identification of the keto group as the source of the problem in Pirenperone, its own witnesses (including Mr. Kennis) indicated that the keto group was the source. Indeed, and further, close prior art compounds, Janssen's Ketanserin and Haloperidol, both had keto groups that underwent such metabolism. *Id.* The overwhelming evidence is that one of skill in the art would have recognized the keto group to be the source of the short half-life of Pirenperone.

Therefore, a person of ordinary skill working in antipsychotic drug development in the early 1980s would have been motivated to replace the keto group of Pirenperone with a different group that would allow for retention of dopamine and serotonin antagonist activity, but which would be metabolized at a slower rate. *Id.* This task would not have been difficult.

E. Identification of the Benzisoxazole as a Means to "Fix" The Short Half-Life

The prior art reported in 1982 that the benzisoxazole-containing drug compound AD-810 "was eliminated from the plasma slowly with a half-life of 60 h[ours]." This value stands in sharp contrast to the loss of activity by Pirenperone (containing a keto group) in less than four hours. *See* FF/CL § III.B.2.g.

One of ordinary skill in the art would have expected compounds containing a benzisoxazole group to possess a longer half-life relative to compounds containing keto groups based on the fact that the body has an enzyme which metabolizes keto groups, but does not have an enzyme which metabolizes benzisoxazole groups. Thus, unlike those containing keto groups, compounds containing benzisoxazole groups are not readily susceptible to metabolic attack in the body, and thus would have been expected by one of ordinary skill to possess a relatively long half-life. *Id.*

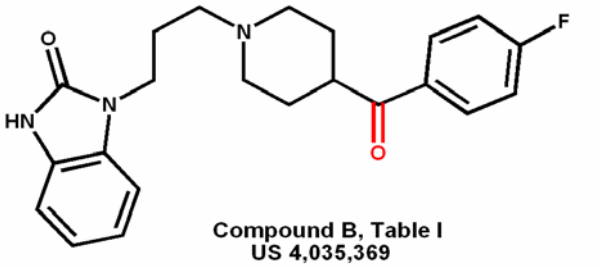
F. Reasonable Expectation of Success

The prior art by Hoechst-Roussel taught that in similar antipsychotic molecules wherein a keto group had been converted to a benzisoxazole, the resulting molecules were active as antipsychotics. One of ordinary skill in the art therefore would have had every expectation (indeed, more than a "reasonable expectation") that when the keto group in Pirenperone had been modified to a

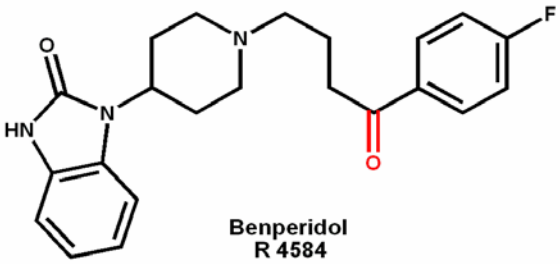
benzisoxazole, that modification would be successful and the resulting molecule also would be active as an antipsychotic. *See* FF/CL § III.B.2.f.

Indeed, scientists at Hoechst-Roussel made and tested "many" compounds containing the benzisoxazole group that "showed potent neuroleptic activity in a variety of pertinent biological assays." In 1982, a team of drug development scientists working at Hoechst-Roussel's laboratories in New Jersey reported to the annual meeting of the American Chemical Society that compounds having the benzisoxazole group were effective as antipsychotics. The Hoescht-Roussel scientists also disclosed a chemical pathway for converting a keto group in an antipsychotic drug to a benzisoxazole group. *Id.*

Indeed Hoechst-Roussel specifically taught the synthesis of antipsychotic drugs that were benzisoxazoles, wherein the antipsychotic drugs were actually the benzisoxazole counterparts to prior art antipsychotic drugs that had a keto group instead of the benzisoxazole. Two such examples are shown in the following figures:

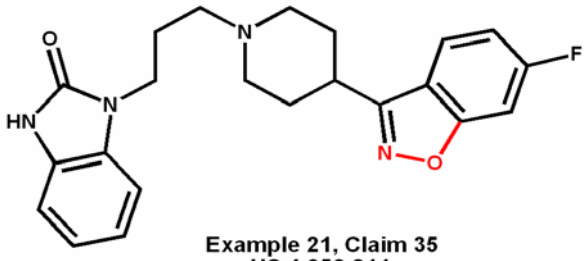


Compound B, Table I
US 4,035,369



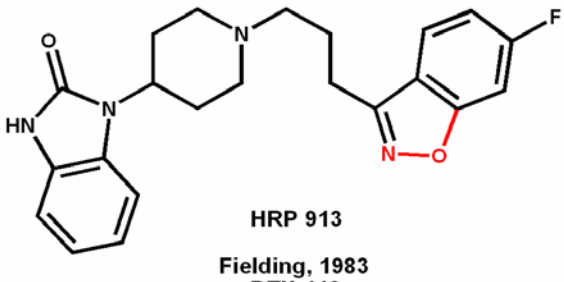
Benperidol
R 4584

Kaiser and Setler, 1981
PX-16



Example 21, Claim 35
US 4,352,811

Compound "11b"
Table VII
J Med Chem (1985)

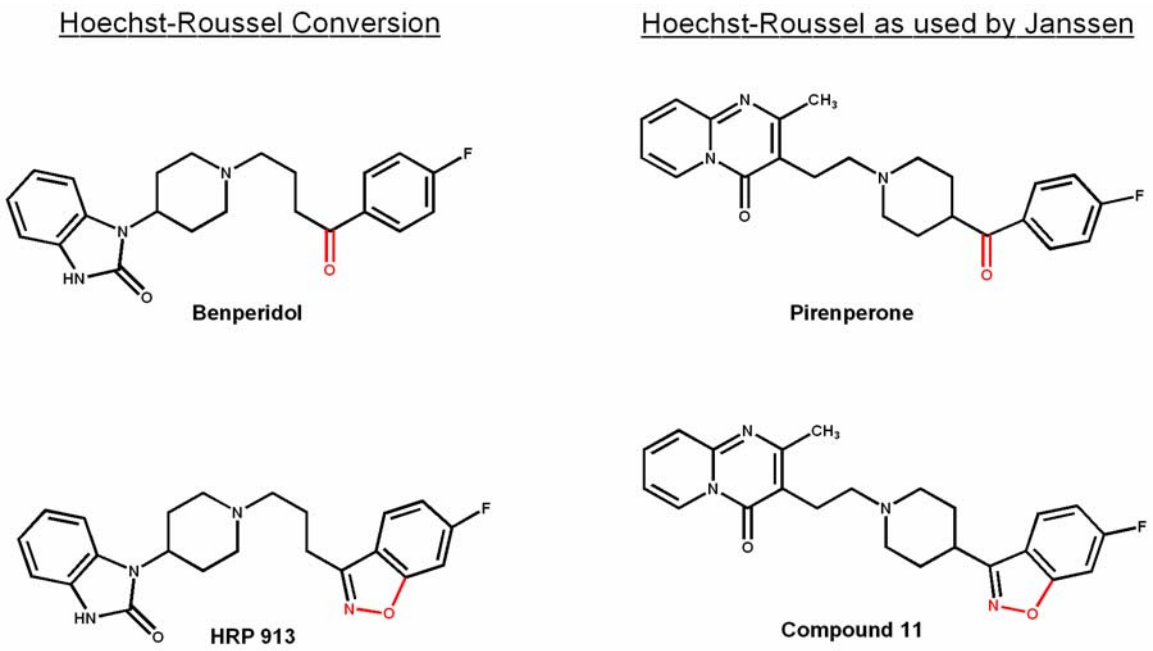


HRP 913

Fielding, 1983
DTX-119

Id.

In the second example, the prior art is actually a Janssen antipsychotic compound (Benperidol) that contains a keto group, the latter subsequently being replaced by Hoechst-Roussel (in or about 1983) with a benzisoxazole group. This prior art teaching by Hoechst-Roussel was followed by Janssen in making Compound 11, as shown in the following figure:



Id.

Accordingly, in order to enhance the duration of action of the parent molecule, there was strong motivation provided to those of ordinary skill in the art working to develop antipsychotics in the early 1980s to chemically modify a keto group to form a benzisoxazole to prevent metabolic conversion. Further, those skilled in the art would have had a reasonable expectation that such a modification would permit the compound to retain activity as an antipsychotic. *Id.*

III. JANSSEN'S ATTEMPTED REBUTTAL

A. Janssen's Position That Pirenperone Was Not an Antipsychotic Is Contrary to Janssen's Own Pre-Litigation View of Pirenperone

Janssen argues that Pirenperone was not an antipsychotic, so there was no motivation for one of skill in the art to modify its structure to develop an

antipsychotic. Janssen's position is litigation driven and stands in sharp contrast to its pre-litigation view of Pirenperone. *See* FF/CL § IV.A.

In 1996, Janssen wrote as a book chapter a "retrospective" relating to the development of antipsychotics over the years. The authors were all from Janssen, including the '663 inventors Mr. Kennis and Mr. Vandenberk, and Dr. Awouters, the latter providing the key declaration during prosecution of the '663 patent. *Id.*

The purpose of the paper was "to better define risperidone-like central activity and its potential occurrence among the *available or experimental neuroleptics*." (emphasis added). The article goes on to state that the authors reviewed the literature to find such compounds (in addition to risperidone) that had high affinity (nanomolar) for both the serotonin receptor ($5HT_2$) and the dopamine receptor (D_2), and also where the serotonin affinity was 5 to 100 fold higher than the dopamine affinity. This review resulted in an identification of a total of 26 compounds. The article continues: "The chemical structures and pharmacology of this *subclass of neuroleptics* were further studied." (emphasis added). *Id.*

Pirenperone is mentioned throughout the article as a member of this select subclass of neuroleptics, *inter alia*, at pages 154, 156, 157, 159, 161, 164 and 168. The article is particularly telling when it places these 26 compounds in groups according to overall chemical structure and states at page 157:

> 5. The pyrimidones: A relatively recent chemical class is made up by the pyrimidones: the benzoylpiperidines *pirenperone* and setoperone

> and the benzisoxazoles *risperidone* and ocaperidone.

(emphasis added). *Id.*

It is clear that at least the inventors believed that Pirenperone was not only properly classified as a neuroleptic (*i.e.*, an antipsychotic), but that Pirenperone belongs in the same chemical class of neuroleptics as Risperidone. *Id.*

Plaintiffs' argument that Pirenperone did not exhibit antipsychotic properties also ignores reality. The properties known in the prior art about Pirenperone pointed to its use as an antipsychotic. Most telling, the prior art teachings about Pirenperone actually went much further in establishing Pirenperone as an antipsychotic than do the teachings in the '663 patent with respect to Compound 11, as shown by the following table. *Id.*

Comparison of Pirenperone and Compound 11		
	Pirenperone	Compound 11
1. Dopamine Receptor Antagonist	√	√
2. Passes Blood-Brain Barrier	√	√
3. Safe to Use in Humans	√	?
4. Does Not Cause EPS	√	?
5. Serotonin Receptor Antagonist	√	√
6. Long Duration of Action	⊗	?

B. Janssen's Position That Those of Skill in the Art Would Not Have Been Motivated to Modify the Structure of Pirenperone Because it Did Not Possess Anticholinergic Properties Is Not Supported

Janssen further posits that those of ordinary skill in the art would not have been motivated to modify the structure of Pirenperone because it did not possess